Original Paper

The Association Between Adiponectin, Serum Uric Acid and Urinary Markers of Renal Damage in the General Population: Cross-Sectional Data from the Tromsø Study

Marit D. Solbu[a,b]   Jon V. Norvik[b]   Hilde M. Storhaug[b,c]   Bjørn O. Eriksen[a,b]
Toralf Melsom[a,b]   Anne Elise Eggen[d]   Svetlana N. Zykova[b,c]   Jens B. Kronborg[b,e]
Trond G. Jenssen[b,f]

[a]Section of Nephrology, University Hospital of North Norway; [b]Metabolic and Renal Research Group, UiT The Arctic University of Norway; [c]Centre for Clinical Research and Education, University Hospital of North Norway; [d]Epidemiology of Chronic Diseases Research Group, UiT The Arctic University of Norway, Tromsø; [e]Department of Immunology and Transfusion Medicine, Innlandet Hospital Trust, Lillehammer; [f]Department of Transplant Medicine, Oslo University Hospital, Oslo, Norway

Abstract
Background/Aims: Uric acid may cause renal damage, whereas adiponectin in some studies has been reported to have renoprotective properties. The renoprotective role of adiponectin under the influence of hyperuricemia has not been explored. We assessed the cross-sectional association between adiponectin, serum uric acid (SUA) and urinary biomarkers of glomerular and tubular damage (albumin-creatinine ratio [ACR] and N-acetyl-β-D-glucosaminidase-creatinine ratio [NAG-CR]) in a large cohort from a general population. *Methods:* Three urine specimens from 7062 persons, participating in the Tromsø Study, were collected. The adjusted associations between adiponectin and SUA as independent variables, and ACR ≥1.13 mg/mmol (albuminuria) and the upper gender specific 15 percentile of NAG-CR (high NAG-CR) as dependent variables, were assessed. *Results:* Mean (standard deviation) age of the participants was 63.5 (9.2) years. Adiponectin was positively associated with albuminuria and high NAG-CR. SUA was associated with albuminuria (odds ratio [OR] 1.13; 95% Confidence Interval [CI] 1.05-1.21 per 59 µmol/L increase), but not with NAG-CR. There were no statistically significant interactions between SUA and adiponectin. *Conclusions:* Unexpectedly, adiponectin was

Marit D. Solbu

Section of Nephrology, Division of Internal Medicine, University Hospital of North Norway, N-9038 Tromsø (Norway)
Tel. +4791864376, Fax +4777669416, E-Mail marit.solbu@unn.no

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positively associated with both urinary markers of renal damage. SUA was positively associated with albuminuria only. SUA and adiponectin added little beyond traditional cardiovascular risk factors to predict renal damage and did not interact in their associations with the urinary biomarkers. Longitudinal studies are needed before firm conclusions can be made.

Introduction

Hyperuricemia has in many studies been associated with chronic kidney disease (CKD) [1-3]. Uric acid is a strong antioxidant in plasma and at the same time a promoter of oxidative and inflammatory processes [4]. Therefore, the role of uric acid in CKD remains controversial; a causal relationship has been suggested [5, 6], but not confirmed [7, 8]. Adiponectin is a cytokine that is secreted primarily by adipocytes and exerts antidiabetic, anti-inflammatory, cardioprotective [9] and renoprotective [10, 11] effects. However, these effects have not been consistently reported, and subgroup differences appear to exist [12-14].

Increased levels of SUA and low adiponectin are frequently observed in the same high-risk phenotypes, especially in obesity and the metabolic syndrome [15, 16]. The biomarkers have shown significant negative correlation [17], but not in all cohorts [18]. Pharmaceutical agents such as peroxisome proliferator-activated receptor-γ (PPAR γ) agonists and xanthine oxidase inhibitors [19, 20] have been demonstrated to simultaneously decrease SUA and increase adiponectin [21, 22]. Thus, it may be suggested that the two biomarkers share some common pathways. Expanded knowledge of a possible interplay between uric acid and adiponectin in CKD may have therapeutic potential.

Adiponectin tends to be low in persons with low-grade albuminuria [23-25], and increased in more advanced stages of albuminuria and proteinuria [26, 27]. However, studies involving persons with low-grade albuminuria have yielded conflicting results [23, 24, 28], suggesting that the association between adiponectin and urinary albumin excretion (UAE) may vary according to underlying risk. In cross-sectional studies, urinary and serum adiponectin have been shown to be positively associated with tubular dysfunction in diabetic patients [29, 30].

SUA has been demonstrated to be a strong predictor of new-onset micro- and macro-albuminuria in diabetes [31], and an association between baseline SUA and incident elevations in UAE has been found in the general population [32-34]. Since even slightly raised UAE is a risk factor for CKD [35], these associations are relevant. Furthermore, SUA correlates with the morphological severity of tubulointerstitial lesions in patients with IgA nephropathy and normal estimated glomerular filtration rate (eGFR) [36]. In cultured tubular cells, SUA causes apoptosis [37], suggesting that SUA is directly involved in tubulointersitial damage. A possible association between SUA and urinary N-acetyl-β-D-glucosaminidase (NAG) activity was found in a small hypertensive cohort [38].

There have so far been no studies relating SUA and adiponectin to glomerular and tubular dysfunction in the general population.

In this cross-sectional study of a large cohort from the Tromsø Study, we aimed to assess the separate and joint associations between adiponectin and SUA, and urinary biomarkers of glomerular and proximal tubular damage, i.e. UAE measured as albumin-creatinine ratio (ACR), and NAG-creatinine ratio (NAG-CR).

Materials and Methods

Study population

The Tromsø Study is a population-based, prospective study of health issues including risk factors, CVD and CKD in the municipality of Tromsø, Northern Norway [39]. In the present study, data from subjects

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who attended both visits of the sixth (2007-08) survey (Tromsø 6) are presented. The data collection and study population have been described in detail elsewhere [40]. A total of 7307 persons (64% of eligible subjects) participated. Among these, 245 persons had one or more missing values of SUA, adiponectin, ACR and/or NAG-CR and were therefore excluded from the present study. The Regional Committee for Medical and Health Research Ethics and The Norwegian Data Protection Authority approved the study, and all participants gave their informed, written consent.

Measurements

Self-reported information about smoking habits, alcohol intake, leisure physical activity, current medication (yes/no/earlier, and a list of all drugs currently used regularly), presence of diabetes and CVD was collected through a questionnaire that was checked by health personnel at the study site. The questionnaires and variables are available at the Tromsø Study web site (https://uit.no/Content/401052/Questionnaire_T6_1.pdf). Tobacco use was classified as current smokers or not (all others). Alcohol intake was categorised according to frequency of alcohol intake (once a month or less often, twice a month to once a week, 2-3 times a week, or more frequently). Leisure physical activity was dichotomised as active (≥1 hour of physical activity with prominent perspiration or breathlessness per week), or inactive (all others). Verified information about previous myocardial infarction and/or ischaemic stroke was obtained from the Tromsø Study Cardiovascular Disease Registry [41]. Blood pressure was recorded in triplets, and the mean of the two last readings was used in the analyses. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg and/or current use of blood pressure lowering medication. Height, weight and waist circumference were measured, and body mass index (BMI) was calculated [40].

First-void morning urine samples from three consecutive days were collected. Albumin and creatinine were measured in unfrozen urine within 20 hours after collection using an ABX PENTRA autoanalyser (Horiba ABX) and kits from ABX Diagnostics (Montpellier, France). The rest of the urine was stored at -20°C. In 2014-15, NAG was measured by a colorimetric method (with 3-cresolsulfonphthaleyn-N-β-D-glucosaminide, Boehringer Mannheim, Germany) in thawed morning urine samples. The concentration of each urinary biomarker was divided by the creatinine concentration of the same specimen, and the median values of ACR and NAG-CR from the three specimens were used in the analyses. In order to achieve values of similar magnitude for both variables, mg/mmol was chosen as the unit for ACR, whereas NAG-CR was reported in U/g. ACR was dichotomised into "albuminuria", i.e. ACR ≥1.13 mg/mmol, or not albuminuria. The cut-off corresponds to the suggested lower limit for "high normal" ACR in the 2012 CKD definition from KDIGO [42]. There is no generally suggested cut-off for NAG-CR, and in order to classify approximately the same number of participants in the "high NAG-CR" group as in the "albuminuria" group, we applied the gender-specific upper 15 percentile to define the group with high NAG-CR.

A non-fasting blood sample was obtained. SUA was measured by photometry with COBAS® instruments (Roche diagnostics, Switzerland) using an enzymatic colorimetric test, the uricase/PAP method. In 2012, adiponectin was measured in stored serum (-70°C). An ELISA method (DY1065 kit from R&D Systems, Inc., Minneapolis, MN) was used. All samples were analysed in duplicate, and the mean value was used. Two control samples were run for each assay to monitor between-assay variation, and the inter-assay coefficients of variation were found to be 7.89% and 7.74% respectively. Serum creatinine was analysed using an enzymatic method that has been standardised against isotope dilution mass spectroscopy (CREA Plus, Roche Diagnostics, GmbH, Mannheim, Germany). Cystatin C was measured with particle-enhanced turbidimetric immunoassay (Gentian AS, Moss, Norway) using a Modular E analyzer (Roche Diagnostics, Mannheim, Germany). eGFR was calculated according to the CKD-EPI creatinine equation (eGFR$_{cre}$) [43] and the CKD-EPI creatinine-cystatin C equation (eGFR$_{crecys}$) [44]. Serum lipids, glucose and glycosylated haemoglobin A1c (HbA1c) were analysed as previously described[40] [45]. Prevalent diabetes was defined as self-reported diabetes mellitus, self-reported use of antidiabetic medication, HbA1c ≥6.5% or non-fasting plasma glucose >10.0 mmol/L.

Statistical Analysis

Continuous data are presented as mean (±standard deviation [±SD]) or median (interquartile range) as appropriate. We checked the bivariate correlations between SUA, adiponectin, eGFR$_{cre}$, eGFR$_{crecys}$, ACR and NAG-CR. Due to the skewed distribution of some of these biomarkers, Spearman's test was applied. Logistic

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regression analyses were used to assess the cross-sectional, multivariable adjusted associations between adiponectin and SUA as continuous variables, and the dichotomised urinary biomarkers, albuminuria and NAG-CR. Covariates were added block wise, and four models were fitted for each dependent variable. All models were age and gender adjusted. In Model 1 and 2, adiponectin and SUA, respectively, were entered as the only additional covariate. In Model 3, both SUA, adiponectin and eGFR$_{crecys}$, were included. Traditional cardiovascular risk factors and current medication use (systolic blood pressure, waist circumference, cholesterol, triglycerides, HbA1c, current smoking, physical activity, alcohol use, prevalent diabetes, previous myocardial infarction and/or ischaemic stroke, current use of diuretics, blockers of the renin-angiotensin system, lipid lowering drugs, antiplatelet drugs and allopurinol) were added as covariates in Model 4. Non-linearity was tested for using fractional polynomial models. By applying the same regression models, we repeated the analyses in the following subgroups: subjects with hypertension (n=4422), diabetes (n=569) and prevalent CVD (previous myocardial infarction and/or ischaemic stroke; n=559).

We applied c-statistics to estimate the area under receiver-operating-characteristic (ROC) curve (AUC) of a basal model (Model A) that included all the mentioned cardiovascular risk factors as covariates. AUC was also calculated when SUA (Model B) and finally adiponectin (Model C) were added. We did this in order to assess the additional predictive value of SUA and adiponectin for albuminuria and high NAG-CR. The equality of the AUC of the ROC curves in Model B and C compared to Model A was tested.

SUA was dichotomised into hyperuricemia and "normal" SUA according to the gender specific cut-offs applied in the NHANES III and 2007-2008 studies (SUA ≥339 µmol/L for women and ≥416 µmol/L for men) [46]. Reference values for adiponectin vary between methods of analysis, and no generally accepted cut-off suggesting a pathologically low value exists. We chose to dichotomise adiponectin into values below or above the lower gender-specific 15 percentile to ensure approximately the same number of individuals in the low-adiponectin group as in the hyperuricemia group. The cohort was classified into four groups according to whether SUA was unfavourable (hyperuricemia) or "normal", and correspondingly whether adiponectin was unfavourable ("low") or "normal". The group with "normal" SUA and adiponectin served as reference. We used ANCOVA to calculate the adjusted mean log-transformed values of the two urinary biomarkers within the four groups, adjusting for the same covariates used in Model 4 of the logistic regression analyses. Mean log-values of ACR and NAG-CR were back-transformed to obtain the geometric mean of each biomarker in each of the four groups, and 95% confidence intervals (CI) for the geometric mean are presented. Analyses were done using IBM SPSS Statistics software version 22 (IBM Corporation, Armonk, New York) and StataMP 14 (StataCorp LP, Texas).

Results

Study Population
The final cohort included 7062 participants (3030 men; 4032 women). Cardiovascular risk factors were compared between the 245 subjects who attended the second visit of Tromsø 6, but were excluded due to missing values for at least one biomarker of interest, and the 7062 participants. No significant differences were found (data not shown).

Cohort characteristics
The cohort characteristics are presented in Table 1. Mean age was 63.5 (±9.2) years, and mean BMI was in the overweight, but not obese, category. A third of the cohort was on antihypertensive treatment, and 8.1% had diabetes. Among the 569 participants with diabetes, 333 received pharmacological treatment; 209 were using blood sugar lowering tablets (sulfonylurea agents and/ or metformin), 37 used insulin and 87 were treated with a combination of insulin and other blood sugar lowering drugs. Only 343 individuals (4.9%) had ACR in the A2 range or above according to the 2012 KDIGO CKD classification (ACR ≥3.39 mg/mmol; also called micro- or macroalbuminuria) whereas 514 men (17.0%) and 545 women (13.5%) had ACR above the "high normal" cut-off (≥1.13 mg/mmol). In spite of the relatively high age, only 351 participants (5.0%) had eGFR$_{crecys}$ <60 ml/min/1.73 m². Hyperuricemia was found in 484 men (16.0%) and 732 women (16.0%). Only one participant reported regular use of

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a SUA lowering drug other than allopurinol (probenecid). This drug class has therefore not been accounted for in the analyses. The range of adiponectin values in the cohort were 0.30-13.28 µg/mL in men and 0.20-17.00 µg/mL in women.

Correlations

Bivariate correlations between the urinary biomarkers, SUA, adiponectin, $eGFR_{cre}$ and $eGFR_{crecys}$ were all highly significant; the r values are presented in Table 2. SUA and adiponectin were negatively correlated. Although correlations between adiponectin and the urinary biomarkers were significant, they were weak with r <0.15. SUA was also only weakly correlated with ACR and NAG-CR, and the unadjusted correlation between SUA and NAG was negative (r= -0.060; P<0.001). $eGFR_{crecys}$

Table 1. Cohort characteristics, n=7062. The Tromsø Study: Tromsø 6

Characteristics			
Gender, women, n (%)		4032	(57.1)
Age, years		63.5	±9.2
Serum uric acid, µg/L	Men	349	±70
	Women	282	±67
Hyperuricemia, n (%)		1216	(17.2)
Serum adiponectin, µg/mL	Men	2.69	(2.06 - 3.58)
	Women	4.03	(3.00 - 5.44)
Urinary albumin/creatinine ratio, mg/mmol	Men	0.34	(0.15 - 0.78)
	Women	0.37	(0.22 - 0.74)
Albuminuria, n (%)		1059	(15.0)
Urinary NAG/creatinine ratio, U/g	Men	1.61	(0.94 - 2.49)
	Women	2.05	(1.22 - 3.22)
$eGFR_{cre}$, ml/min/1.73 m²		88.1	±14.0
$eGFR_{crecys}$, ml/min/1.73 m²		91.3	±16.5
Systolic blood pressure, mm Hg		140.6	±22.9
Diastolic blood pressure, mm Hg		78.4	±10.6
Body mass index, kg/m²		27.0	±4.2
Waist circumference, cm		95.4	±12.1
Cholesterol, mmol/L		5.76	±1.10
HDL-cholesterol, mmol/L		1.56	±0.45
Triglycerides, mmol/L		1.30	(0.90 - 1.80)
HbA1c, %		5.73	±0.65
Current smoker, n (%)		1297	(18.4)
Alcohol intake at least twice a week, n (%)		1601	(23.1)
Physically active, n (%)		2134	(30.2)
Hypertension, n (%)		4422	(62.6)
Diabetes, n (%)		569	(8.1)
Previous myocardial infarction, n (%)		429	(6.1)
Previous ischemic stroke, n (%)		151	(2.1)
Antihypertensive medication, n (%)		2370	(33.6)
Blockers of the renin-angiotensin system, n (%)		1157	(16.4)
Diuretics, n (%)		1062	(15.0)
Allopurinol, n (%)		46	(0.7)
Lipid lowering medication, n (%)		1353	(19.2)
Antiplatelet medication, n (%)		1098	(15.5)

NAG: N-acetyl-β-D-glucosaminidase. $eGFR_{cre}$ and $eGFR_{crecys}$: estimated glomerular filtration rate according to the CKD-EPI equations based on creatinine and creatinine + cystatin C. HbA1c: glycosylated haemoglobin A1c. Hyperuricemia: serum uric acid ≥339 µmol/L (females) and ≥416 µmol/L (males). Albuminuria: urinary albumin/creatinine ratio ≥1.13 mg/mmol. Hypertension: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure lowering medication.

had a stronger negative correlation to all the urinary biomarkers than $eGFR_{cre}$. Interestingly, the absolute value of the correlations between SUA and both GFR estimates were <0.30 and thus considered weak. Both adiponectin and SUA were positively correlated to age (r=0.20, and r=0.12, respectively; P<0.001).

Multivariable associations between SUA, adiponectin and the urinary biomarkers

There was no non-linear association between adiponectin and the urinary biomarkers. A weak association was found between SUA to the third degree and ACR. A fractional polynomial plot suggested that this association was valid only at extreme values of SUA, and when the 15 observations of SUA ≥600 µmol/L were omitted from the analyses, the non-linear association disappeared.

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Table 2. Spearman's correlations between renal biomarkers. The Tromsø Study: Tromsø 6

	Serum uric acid	Adipo-nectin	ACR	NAG-CR	eGFR$_{cre}$	eGFR$_{crecys}$
Serum uric acid	1					
Adiponectin	-0.36	1				
ACR	0.058	0.052	1			
NAG-CR	-0.060	0.13	0.18	1		
eGFR$_{cre}$	-0.24	-0.12	-0.10	-0.076	1	
eGFR$_{crecys}$	-0.25	-0.13	-0.17	-0.12	0.88	1

All partial correlations were significant with P<0.001. ACR: urinary albumin/creatinine ratio. NAG-CR: urinary N-acetyl-β-D-glucosaminidase/creatinine ratio. eGFR$_{cre}$ and eGFR$_{crecys}$: estimated glomerular filtration rate according to the CKD-EPI equations based on creatinine and creatinine + cystatin C.

Table 3. Odds ratios (OR) for having albuminuria (urinary albumin/creatinine ratio (ACR) ≥1.13 mg/mmol or N-acetyl-β-D-glucosaminidase/creatinine ratio (NAG/crea) in the upper gender-specific 15 percentile. The Tromsø Study: Tromsø 6

	OR for albuminuria	95% Confidence interval	P value	OR for upper 15 percentile of NAG/crea	95% Confidence interval	P value
Model 1						
Adiponectin, per μg/mL	0.99	0.95 - 1.03	0.61	1.05	1.01 - 1.09	0.015
Model 2						
SUA, per 59 μmol/L	1.29	1.22 - 1.37	<0.001	1.00	0.95 - 1.06	0.87
Model 3						
Adiponectin, per μg/mL	1.01	0.97 - 1.05	0.54	1.04	1.01 - 1.08	0.026
SUA, per 59 μmol/L	1.20	1.13 - 1.28	<0.001	0.95	0.90 - 1.02	0.15
eGFR$_{crecys}$ per 5 mL/min/1.73 m2	0.92	0.90 - 0.95	<0.001	0.93	0.91 - 0.96	<0.001
Model 4						
Adiponectin, per μg/mL	1.11	1.06 - 1.16	<0.001	1.09	1.05 - 1.14	<0.001
SUA, per 59 μmol/L	1.13	1.05 - 1.21	0.001	0.95	0.88 - 1.02	0.13
eGFR$_{crecys}$ per 5 mL/min/1.73 m2	0.94	0.91 - 0.97	<0.001	0.94	0.91 - 0.97	<0.001

All models are age and gender adjusted. The following additional variables are included as independent variables: Model 3, estimated glomerular filtration rate (eGFR$_{crecys}$) calculated using the combined creatinine and cystatin C CKD-EPI equation; Model 4, as Model 3 plus previous myocardial infarction and/or ischemic stroke, prevalent diabetes, current smoking, alcohol intake (categorised into once a month or less, 2-4 times a months, once a week or more), ≥1 hour of excercise per week, systolic blood presssure, waist circumference, cholesterol, triglycerides, glycosylated haemoglobin A1, current use of allopurinol, lipid lowering drugs, antiplatelet drugs and blockers of the renin-angiotensin system and diuretics.

The adjusted odds ratios (ORs) for albuminuria (ACR ≥1.13 mg/mmol) and NAG-CR (upper 15 percentile) by adiponectin and SUA as predictor variables are shown in Table 3. In age and gender adjusted models, higher adiponectin was significantly associated with higher NAG-CR, but not with albuminuria, whereas SUA was associated with albuminuria only. When both adiponectin and SUA were entered into the same model and adjusted for age, gender and eGFR$_{crecys}$, the estimates were not substantially changed. With further adjustment for cardiovascular risk factors and medication use, the association between SUA and albuminuria was attenuated, whereas the associations between adiponectin and both urinary biomarkers were strengthened. In the fully adjusted model (Model 4), 1 μg/mL increase in adiponectin was associated with a 11% and 9% increased risk of albuminuria and high NAG-CR, respectively. There was no statistically significant interaction between SUA and adiponectin for the association with ACR and NAG-CR (P=0.36 and 0.56). There was a significant interaction between SUA and gender for the prediction of ACR (P=0.002). In gender stratified analyses SUA was a significant predictor of ACR in men only (OR per 59

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Table 4. Area under the ROC curve (AUC) for the prediction of increased albumin creatinine ratio (ACR) ≥1.13 mg/mmol and the upper 15 percentile of N-acetyl-β-D-glucosaminidase creatinine ratio (NAG-CR), using different prediction models. The Tromsø Study: Tromsø 6

	ACR ≥1.13 mg/mmol		Upper 15 percentile of NAG-CR	
AUC Model A (95% Confidence Interval)	0.724	(0.706 - 0.741)	0.619	(0.599 - 0.638)
AUC Model B (95% Confidence Interval)	0.725	(0.707 - 0.742)	0.618	(0.599 - 0.638)
AUC Model C (95% Confidence Interval)	0.728*	(0.710 - 0.746)	0.628*	(0.608 - 0.647)

Model A: gender, age, previous myocardial infarction and/or ischemic stroke, prevalent diabetes, current smoking, alcohol intake (categorised into once a month or less, 2-4 times a months, once a week or more), ≥1 hour of exercise per week, systolic blood pressure, waist circumference, cholesterol, triglycerides, glycosylated haemoglobin A1, current use of allopurinol, blockers of the renin-angiotensin system, lipid lowering drugs, antiplatelet drugs and diuretics.
Model B: Model A + serum uric acid. Model C: Model B + serum uric acid and adiponectin.
*P<0.05 for difference between Model A and Model C

Table 5. Urinary biomarkers according to classification of serum adiponectin and uric acid (SUA). Adiponectin is classified as low (lower gender specific 15%) or normal (upper gender specific 85%); SUA is classified as hyperuricemia[a] or normal. The Tromsø Study: Tromsø 6

	Normal adiponectin/ normal SUA (n=5075) (reference group)		Low adiponectin/ normal SUA (n=771)		Normal adiponectin/ hyperuricemia (n=922)		Low adiponectin/ hyperuricemia (n=294)	
	Geometric mean	95% CI[b]	Geometric mean	95% CI[b]	Geometric mean	95% CI[b]	Geometric mean	95% CI[b]
Age and gender adjusted ACR, mg/mmol	0.40	0.38 - 0.41	0.43	0.40 - 0.46	0.54[d]	0.51 - 0.58	0.56[d]	0.49 - 0.63
Multivariable adjusted ACR[c], mg/mmol	0.41	0.40 - 0.43	0.38	0.35 - 0.41	0.47[d]	0.43- 0.50	0.43	0.37 - 0.49
Age and gender adjusted NAG-CR, U/g	1.55	1.51 - 1.60	1.44	1.34 - 1.56	1.57	1.47 - 1.69	1.36[d]	1.20 -1.55
Multivariable adjusted NAG-CR[c], U/g	1.57	1.53 - 1.62	1.38[d]	1.28 - 1.50	1.48	1.37 - 1.61	1.21[d]	1.06 - 1.38

ACR: urinary albumin creatinine ratio. NAG-CR: urinary N-acetyl-β-D-glucosaminidase (U/L) to creatinine (g/L) ratio.
[a]Hyperuricemia wa defined as ≥339 μmol/L in women and ≥416 μmol/L in men. [b]95% confidence interval (CI) of the geometric mean. [c]Adjusted values: adjusted for the following covariates: age, gender, systolic blood pressure, waist circumference, creatinine and cystatin C based estimated glomerular filtation rate (CKD-epi equation), cholesterol, triglycerides, glycosylated hemoglobin A1, prevalent diabetes, prevalent myocardial infarction and/or ischemic stroke, current smoking, frequency of alcohol intake, physical activity, current use of inhibitors of the renin-angiotensin system, diuretics, lipid lowering drugs, antiplatelet drugs and/or allopurinol. [d]P<0.05 for comparison with the reference group.

μmol/L increase was 1.18; 95% CI 1.07-1.30 in men and 1.09; 95% CI 0.98-1.21 in women).

eGFR$_{crecys}$ was negatively associated with albuminuria and NAG-CR in the upper 15 percentile.

The associations between adiponectin and SUA and the urinary biomarkers were not substantially different in subgroup analyses that included hypertensive subjects (n=4422) or subjects with prevalent CVD (n=559). However, when the same models were run in the subgroup with diabetes (n=569), neither adiponectin nor SUA was associated with any of the urinary biomarkers (data not shown).

AUC of ROC curves

The AUC of ROC curves for predicting albuminuria and high NAG-CR did not increase significantly when SUA was added to the baseline model of covariates. Further addition of adiponectin slightly, and significantly, increased the predictive value for both biomarkers (Table 4).

Adjusted values for the urinary biomarkers

Multivariable adjusted geometric means of both urinary biomarkers for the groups based on "normal" or unfavourable SUA and adiponectin, are displayed in Table 5. Although the between-group differences were reduced with multivariable adjustment, ACR remained higher in the group with high SUA and "normal" adiponectin compared to the reference group

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with "normal" SUA and adiponectin (P=0.04). ACR in the two remaining groups did not differ significantly from the reference group. The geometric mean of NAG-CR was lower in the two groups with low adiponectin compared to reference (P=0.03 and P=0.002, respectively), whereas NAG-CR in the group with unfavourable SUA only was not significantly different from the reference group.

Discussion

In this large cohort from the general population, we found that although SUA and adiponectin were correlated, they were differentially associated with two urinary biomarkers of glomerular and tubular dysfunction, respectively. Firstly, SUA was positively associated with albuminuria, but not related to high NAG-CR. Secondly, in this overall low-risk cohort with a normal mean eGFR and low-grade albuminuria, we expected to find a negative association between adiponectin and the urinary biomarkers. To the contrary, an independent and positive association was found. The associations were essentially the same in subgroup analyses of hypertensive subjects and participants with prevalent CVD, but not in the diabetic subgroup. Thirdly, there were no statistically significant interactions between SUA and adiponectin for the associations with any of the urinary biomarkers. Finally, although c-statistics revealed that SUA and adiponectin added significantly to the prediction of albuminuria and high NAG-CR beyond traditional cardiovascular risk factors and eGFR, the contribution was small.

Although low adiponectin repeatedly has been demonstrated to be associated with low-grade albuminuria [23, 24, 47], this finding has not been consistent [28]. However, to our knowledge, a positive association between adiponectin and low-grade UAE in a low-risk cohort has not previously been reported. The similar association between adiponectin and both urinary biomarkers strengthens the assumption that the result was not a spurious finding and a type I error. It has been suggested that the elevated serum adiponectin observed in patients with advanced stages of CKD [48, 49] is a compensatory response to glomerular damage or adiponectin resistance [50] or secondary to reduced clearance [51]. In our low-risk cohort, we did not expect these mechanisms to be important, but we cannot exclude their involvement. Moreover, although age was adjusted for, a phenomenon related to aging is another possible explanation for the positive association observed in this cohort of relatively old individuals; adiponectin increases with age [52] and is associated with adverse outcome in the elderly [53].

NAG is a protein that is not filtered through the glomerulus, and all NAG present in the urine has been secreted by proximal tubular cells. Therefore, NAG is considered a marker of tubular dysfunction or damage [54, 55]. NAG has been demonstrated to predict vascular disease in patients with diabetes [56], and we recently published that NAG-CR was independently, though weakly, associated with CVD and all-cause mortality in the general population [41]. We also showed that increasing NAG-CR was related to a more adverse cardiovascular risk profile. Despite these relationships, the present study does not support a connection between SUA and early proximal tubular damage in the general population. Based on the lack of association between SUA and NAG-CR, we suggest that the positive association between SUA and ACR in this low-risk populations is a reflection of generalised endothelial dysfunction [57] or slight glomerular damage, rather than low-grade tubular damage.

Our hypothesis that there may be an interaction between SUA and adiponectin in their association with low-grade kidney damage was not supported by the present results, neither in the entire cohort nor among hypertensive subjects and participants with prevalent CVD. However, it should be noted that the ranges of important laboratory measurements, especially eGFR, ACR, and adiponectin, were relatively narrow. Therefore, extrapolation of the results to patients with more extreme values should not be done. In a recently published, large cohort study it was demonstrated that visceral fat area, assessed by multi-frequency bioimpedance

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analysis, was strongly associated with CKD, defined as eGFR <60 mL/min/1.73 m^2, as well as with SUA [58]. Adiponectin was not measured in this study, but low adiponectin and visceral fat area has previously been shown to be highly intercorrelated [16]. Thus, our findings do not exclude the possibility of an interaction in subgroups, and SUA and adiponectin may act synergistically with regard to more advanced stages of CKD [58-60], and in subjects with less favourable values of SUA, adiponectin and the urinary biomarkers. This matter is of relevance since pharmaceutical agents such as PPAR γ agonists [21, 22] and some blockers of the renin-angiotensin system [61, 62] are known to simultaneously decrease SUA and increase adiponectin, and thus these biomarkers may share common pathways. Therefore, this issue should be addressed further through longitudinal studies.

The main strengths of the present study were the large cohort size, high attendance rate, large number of covariates and the use of three urine samples to reduce the day-to-day variation of protein excretion. Albumin was measured in fresh urine. However, NAG was measured after prolonged storage of the urine, which may have affected the results. The cohort consisted almost exclusively of middle-aged to old Caucasian individuals, which restricts the generalisability. The cross-sectional design of the study was its main limitation, and the associations should be reassessed in cohorts with short- and long-term follow-up, and related to hard endpoints. Furthermore, there is a complex interplay between uric acid, adiponectin and other cytokines, including monocyte chemotactic protein-1 [60], and interleukins, and these biomarkers would have added valuable information to the study. However, for logistic and financial reasons, only adiponectin was analysed in this large cohort, which is a limitation.

Conclusion

In a large cohort of middle-aged to elderly persons from the general population, we found no statistically significant interaction between adiponectin and SUA in their association with two urinary biomarkers of kidney damage, and their individual and joint contribution to the prediction of the biomarkers was small. Unexpectedly, adiponectin was positively associated with all the urinary biomarkers, and SUA was positively associated with ACR only. The relationships between promoting and protective factors and low-grade kidney damage is complex, and follow-up studies, as well as studies that include several biomarkers, should be conducted.

Disclosure Statement

None.

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